Table 1—*Logistic regression model testing adjusted association between serum cholesterol group and depression (defined as score on geriatric depression scale >10) in 476 elderly hospital patients*

	No of patients	Odds ratio (95% confidence interval)
Serum cholesterol (mmol/l):		
≥6.20	60	1.0*
4.14-6.19	313	2.0 (1.1 to 3.6)
≤4.13	103	2.7 (1.3 to 5.5)
Age ≥80	215	1.1 (0.7 to 1.6)
Women	333	1.8 (1.1 to 2.7)
Living alone	163	1.0 (0.7 to 1.5)
≥6 Diseases	279	0.7 (0.4 to 1.1)
Impaired function†	224	1.7 (1.1 to 2.5)
Cognitive impairment‡	172	1.9 (1.2 to 2.9)
Malnutrition§	260	0.7 (0.5 to 1.2)

*Reference group.
†Score on Tinetti scale <18. ‡Score on minimental state examination <22. §Score on prognostic nutritional index >35.

Data in this study were taken from 476 elderly patients consecutively admitted to our unit over 12 months (mean age 78.8 (SD 7.4); 70% women). A multidimensional evaluation, including information on demographics, physical health, cognitive and affective status, functional ability, and social support, was performed on the third day after admission with a standard protocol. Cognitive status was evaluated by the Folstein mini-mental state examination, depressive symptoms with the geriatric depression scale,[2] and functional disability with the Tinetti balance and gait scale. Nutritional status was assessed by Mullin's prognostic nutritional index, which considers the serum albumin concentration, triceps skinfold thickness, serum transferrin concentration, and results of skin sensitisation tests. Somatic health was assessed as the number of diseases.

The patients were stratified in three groups of decreasing serum cholesterol concentrations: ≥6.20, 4.14-6.19, and ≤4.13 mmol/l. Mean scores on the geriatric depression scale across the three groups were, respectively, 11.3 (6.5), 13.3 (6.3), and 14.1 (6.9) mmol/l (P=0.025 on analysis of variance). The association of serum cholesterol groups with depression (defined as a score on the geriatric depression scale of >10) was tested in a multiple logistic regression model in which confounding by age, sex, somatic health, poor cognition, malnutrition, disability, and living alone could be controlled for. Table 1 shows that the risk of depression was greater in the group with the lowest serum cholesterol concentration even after the potential confounders were considered.

Although these results cannot confirm the mechanism proposed by Steegmans and colleagues to explain the relation between low serum cholesterol concentration and depression, the strength of the association that we found suggests that it may be clinically relevant in elderly people. Our data and those of Steegmans and colleagues need further confirmation, particularly in the light of previously reported conflicting data.[3]

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Other studies have been done in humans and monkeys

EDITOR,—Paul H A Steegmans and colleagues assert that theirs was the first study in humans to investigate the relation of serum cholesterol concentration to metabolism of serotonin and that only one study in monkeys has done so.[1] However, two studies in humans bear on this issue, as does one study in primates that they fail to cite.

Ringo *et al* found a non-significant trend towards an increased cerebrospinal fluid concentration of 5-hydroxyindoleacetic acid (a central metabolite of serotonin thought to gauge turnover of serotonin) with high cholesterol concentration in psychiatric patients and staff.[2] The 23% higher mean 5-hydroxyindoleacetic acid concentration in subjects with a high cholesterol concentration is comparable in size, though not significance, to the 19% higher (arithmetic) mean peripheral serotonin concentration in Steegmans and colleagues' study. Anderson *et al* found significantly reduced plasma tryptophan concentrations in people placed on diets to induce weight loss.[3] Women, who were placed on a lower fat diet than men (25% energy from fat *v* 35%), showed a greater reduction in tryptophan concentrations and a significant change in hormonal measures of central serotonin.

In primates Muldoon *et al* documented a 31% higher prolactin response to fenfluramine (a hormonal measure of combined presynaptic and post-synaptic central serotonin activity) in monkeys with high cholesterol concentrations than in those with low cholesterol concentrations due to dietary intervention. This effect was significant.[4]

Rather than being the first study in humans and the second in primates, the study by Steegmans and colleagues is an important addition to a growing body of evidence suggesting a connection between cholesterol and central serotonin that may help to mediate an association between low(ered) cholesterol and violence.

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Authors' reply

EDITOR,—Hanno Pijl and colleagues suggest that the higher alcohol intake in our reference group could explain the higher plasma serotonin concentration in the group. The study they refer to, however, is an in vitro study. Although platelet serotonin concentrations are generally decreased in alcoholic subjects,[1 2] the effects on plasma serotonin concentrations are unknown. In one study platelet uptake of serotonin was increased in alcoholic subjects, without modifications of the paroxetine binding site.[3] The results are therefore equivocal. Importantly, adjustment for use of alcohol did not materially change our findings.

Although plasma free serotonin concentrations are increased in peripheral vascular disease, this disease cannot have been responsible for the observed association between low cholesterol and serotonin concentrations in our study: the prevalence of cardiovascular disease (including symptomatic peripheral vascular disease) was even lower in the reference group (4%) than the group with low cholesterol concentrations (9%). Furthermore, the prevalence of cardiovascular risk factors (hypertension) was similar in the two groups.

Pijl and colleagues state that the mechanisms responsible for the release and degradation of serotonin differ considerably between peripheral tissue and brain. This may be true for release of serotonin but is not for its degradation. Removal of free serotonin from the plasma or the synaptic cleft occurs through uptake by platelets or the neurone, respectively. The degradation in both instances takes place mainly in other cells—namely, the cells of the liver and lung and the neuroglial cells, respectively. Thus similarities exist in the mechanisms by which the periphery and the brain regulate the action of serotonin.

Pijl and colleagues conclude that the plasma free serotonin concentration is probably determined by factors other than cholesterol and does not reflect synaptic availability. As we mentioned, however, the finding of lower plasma serotonin concentrations in men with low cholesterol concentrations indicates that the metabolism of serotonin is altered in these subjects, especially as no alternative explanation for the observed association exists. If plasma serotonin concentrations do correlate with the concentrations in the synaptic cleft, this may explain the higher incidence of suicide in people with low cholesterol concentrations.

The study by Renzo Rozzini and colleagues provides important additional evidence for the association between naturally occurring cholesterol concentrations and depression in elderly people. It would have been even more interesting if they had studied measures of serotonin metabolism.

The findings of Ringo *et al*, mentioned by Beatrice Golomb, are in line with our results. In contrast to our population based study, their study was restricted to psychiatric patients. The study by Anderson *et al* did not address the relations between naturally occurring cholesterol concentrations and metabolism of serotonin.

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